compounds with any substitution at this position, let alone the methyl group as in the claimed compounds.

Applicants previously filed a Declaration under 37 C.F.R. § 1.132 of William S. Caldwell, which distinguished the claimed compounds from the compounds disclosed by Dull. If the Examiner believes that the following arguments will not be persuasive unless submitted in a further Declaration under 37 C.F.R. § 1.132 , the Examiner is encouraged to contact Applicants' undersigned representative to provide Applicants with an opportunity to file such a Declaration before issuing a further Office Action.

The previously submitted Declaration outlined several important differences between compounds with a methylene ($-CH_2$) group (the Dull patent) or a $-CH(CH_3)$ group (as presently claimed) at a position alpha to the amine group. The differences relate to the biological and pharmacokinetic characteristics of the compounds, including their high affinity for the relevant receptor (the $\alpha4\beta2$ receptor), their ability to elicit functional response at the receptor, and their resistance to metabolic clearance. Accordingly, the Declaration demonstrated the superiority of pyridinyl compounds with an alpha methyl group (*i.e.*, alpha to the amine group) versus pyridinyl compounds without an alpha methyl group. The Office Action raised three issues, all of which are addressed herein.

The first issue raised was that the Declaration shows the effect of alpha methyl substitution on pyridinyl compounds, whereas Applicants are using this data to support a showing of non-obviousness with respect to pyrimidinyl compounds. Applicants assert that the claimed alpha methyl pyrimidine has improved metabolic clearance relative to a similar pyrimidinyl compound that does not include the alpha methyl substituent.

The effect of the alpha methyl substitution is believed to involve steric hindrance to amine oxidases that otherwise deaminate the amine group at the adjacent position. This effect would not be expected to be adversely effected by a substitution of the heteroaryl ring at a position far removed from the relevant carbon (*i.e.*, the carbon to which both the amine and methyl group are attached). Clearly, the alpha methyl group provides no less steric hindrance to the directly adjacent amine group when a pyridine or pyrimidine ring is present at a position three carbons away from the alpha position. There is no sound scientific reason to doubt that alpha methyl pyridines would have improved metabolic clearance and alpha methyl pyrimidines would

not. Applicants further assert that the claimed compounds bind with suitable affinity at the relevant receptor. Accordingly, the claimed compounds have both suitable binding affinity and suitable metabolic clearance.

The Office Action's assertion that since the pyridinyl compounds are known in the art, they can be used to reject the pyrimidinyl compounds, is somewhat unclear. Dull teaches both pyridinyl and pyrimidinyl compounds, but in both cases, the compounds lack the alpha methyl substitution present in the claimed compounds.

The second issue was whether the claimed compounds that are in the form of cis-isomers also benefit from the claimed superior properties. Applicants respectfully assert that they do. In some embodiments, the cis-isomers (and related cis-isomers that do not include an alpha methyl group) do not bind as tightly to the relevant receptor as the corresponding trans-isomers. However, the compounds demonstrate suitable binding affinity, and, indeed, the Office Action does not appear to question this point. The only issue appears to be whether the cis-isomers also benefit from the superior resistance to metabolic clearance. The double bond is cis or trans depending on the relative orientation of the pyrimidine ring. As discussed above, the pyrimidine ring is far enough removed from the alpha methyl group (which, again, is believed to hinder deamination of the directly adjacent amine group via steric hindrance) that it does not adversely effect the methyl group's ability to hinder deamination. The Office Action does not provide any scientific basis for believing that the cis compounds would not also benefit from the superior resistance to metabolic clearance.

The third issue was that the Declaration shows that the R alpha methyl isomer is about as active as the unsubstituted compound, and in the Examiner's view, this does not support a finding of unexpected/superior properties. Applicants respectfully disagree with the Examiner's position. Binding is one property, and metabolic clearance is another. The issue is not whether the alpha methyl compounds bind more tightly to the receptor than similar compounds that are not substituted with an alpha methyl group. The issue is that the compounds with alpha methyl substitution offer superior resistance to metabolic clearance and suitable binding to the relevant receptor.

Even if the alpha methyl compounds bind the relevant receptor with similar binding constants as the alpha CH_2-substituted compounds, the alpha methyl compounds have totally

different metabolic properties, and have significantly improved *in vivo* half-lives. That feature is sufficient to demonstrate that the claimed compounds are non-obvious over prior art compounds that did not include alpha methyl substitution.

The previously submitted Declaration demonstrated that, in light of problems associated with the metabolism of the N-methyl-4-(3-pyridinyl)-3-buten-1 amine compound described in Dull, an effort was made to identify compounds that possessed both good binding/functional characteristics and good pharmacokinetic profiles. During the course of the research, which involved forming a plurality of compounds with substituents at varying positions, the results (and the isolation of metabolites) indicated that the problem might involve monoamine oxidase activity at the secondary amine side chain. After identifying the problem, the next step was to provide a (non-obvious) solution to the problem. Many proposed solutions to this problem overcame the metabolic issue, but failed to provide adequate binding to the relevant receptor. However, one solution not only overcame the problem, but also retained the binding to the relevant receptor. This solution came in the form of providing an alpha alkyl (in this case, alpha methyl) substituent.

The alpha methyl compounds showed improved metabolic characteristics and retained binding at the $\alpha 4\beta 2$ receptor. The unexpected result is that the compounds have an improved overall combination of biological and pharmacokinetic characteristics (high affinity for the receptor, ability to elicit functional response at the receptor and resistance to metabolic clearance). These characteristics make the claimed α-methyl compounds significantly better drug candidates than the unsubstituted analogs described in the Dull patent. The claimed compounds are an example of such compounds, and are therefore non-obvious in view of Dull.

Accordingly, the Examiner is respectfully requested to withdraw the obviousness rejections.

Rejections Under the Judicially Created
Doctrine of Obviousness-type Double Patenting

Claim 12 has also been rejected under the judicially created doctrine of obviousness-type double patenting as obvious in view of claims 15-21 of co-pending U.S.S.N. 09/973,419 and over claim 8 of Dull. As discussed above, the claims are non-obvious over Dull, so the

obviousness-type double patenting rejection should be withdrawn. Co-pending U.S.S.N. 09/973,419 has now been allowed, and Applicants now enclose a terminal disclaimer.

The Examiner is invited to contact the undersigned if he has any questions or further comments.

Respectfully submitted,

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